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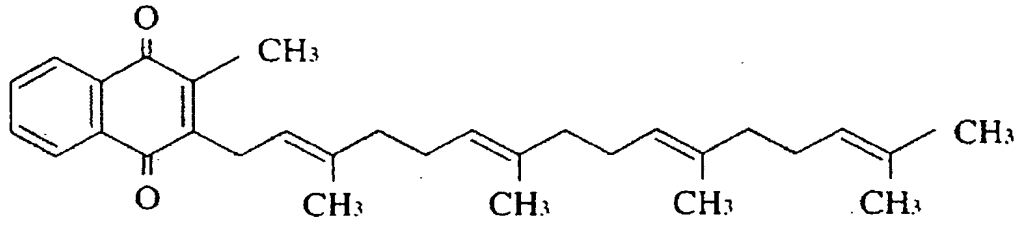
最終頁に続く

(54)【発明の名称】キノン系肝疾患治療剤

(57)【要約】
【課題】有用な肝疾患治療剤は未だ提供されておらず、特に門脈内腫瘍浸潤（ＰＶＩ）の発生抑制による肝疾患治療剤は提供されていなかった。
【解決手段】本件出願の肝疾患治療予防剤は、メナテトレノンを有効成分として含む優れた肝疾患治療予防剤である。本肝疾患治療予防剤は、肝癌、特にＤＣＰ（Ｄｅｓ－γ－Ｃａｒｂｏｘｙ　Ｐｒｏｔｈｒｏｍｂｉｎ）陽性肝癌に対して有効である。本肝疾患治療予防剤は門脈内腫瘍浸潤（ＰＶＩ）の発生抑制剤である。肝癌治療後の予後の改善に顕著な効果を有する。肝癌の再発抑制剤としても優れた効果を有する。
【選択図】　なし

【特許請求の範囲】
【請求項１】
メナテトレノンを有効成分として含む肝疾患治療・予防剤。
【請求項２】
肝疾患が肝癌である請求項１記載の剤。
【請求項３】
肝癌がＤｅｓ－γ－Ｃａｒｂｏｘｙ　Ｐｒｏｔｈｒｏｍｂｉｎ（ＤＣＰ）陽性肝癌である請求項２記載の剤。
【請求項４】
肝癌治療後の予後を改善する請求項１乃至請求項３のいずれか１項に記載の剤。
【請求項５】
門脈内腫瘍浸潤（ＰＶＩ）の発生抑制剤である請求項４記載の剤。
【請求項６】
メナテトレノンを有効成分として含む門脈内腫瘍浸潤（ＰＶＩ）の発生抑制剤。
【請求項７】
メナテトレノンを有効成分として含む肝癌治療後の生存率改善剤。
【請求項８】
メナテトレノンを有効成分として含む肝細胞癌の再発抑制剤。
【請求項９】
メナテトレノンを有効成分として含むＤＣＰ低下剤。
【請求項１０】
メナテトレノンを有効成分として含む医薬を患者に有効量投与することを特徴とする門脈内腫瘍浸潤（ＰＶＩ）の予防方法。
【請求項１１】
メナテトレノンを有効成分として含む医薬を患者に有効量投与することを特徴とする肝細胞癌の再発抑制法。
【請求項１２】
メナテトレノンを有効成分として含む医薬を患者に有効量投与することを特徴とする血中ＤＣＰ量の調節法。
【請求項１３】
ＰＶＩの発生抑制剤製造のためのメナテトレノンの使用。
【請求項１４】
肝細胞癌の再発抑制のためのメナテトレノンの使用。
【請求項１５】
ビタミンＫ類を有効成分として含む肝疾患治療・予防剤。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】
本発明は、メナテトレノンを有効成分とする肝疾患治療剤、より詳しくは肝癌予後改善剤に関する。
【０００２】
【従来の技術】
肝細胞癌（ｈｅｐａｔｏｃｅｌｌｕｌａｒ　ｃａｒｃｉｎｏｍａ、以下、「ＨＣＣ」と称する。）患者は高率に門脈浸潤（Ｐｏｒｔａｌ　Ｖｅｎｏｕｓ　Ｉｎｖａｓｉｏｎ、以下、「ＰＶＩ」と称する。）をきたすことが知られており、一旦ＰＶＩが発生すると予後は極めて不良である。ここで、ＨＣＣ患者におけるＤｅｓ－γ－Ｃａｒｂｏｘｙ　Ｐｒｏｔｈｒｏｍｂｉｎ（以下、「ＤＣＰ」と称する。）の高値が、その後のＰＶＩ進展と密接に関連することが知られている（Ｋｏｉｋｅ　Ｙ．　Ｃａｎｃｅｒ　２００１；９１：５６１－９）。ここで、ＤＣＰとは、正常な凝固活性を持たないプロトロンビンで、ビタミンＫ（以下、「ＶＫ」と称する。）が欠乏した状況で増えることが知られており、ＶＫの欠

乏・ＶＫの吸収障害のマーカーとして用いられるタンパク質である。
一方で、ＤＣＰ高値ＨＣＣ患者に対しＶＫを投与すると血清のＤＣＰ値が低下すること（Ｃａｎｃｅｒ　１９９２；６９：３１－８）、ｉｎ　ｖｉｔｒｏでＤＣＰ産生のＨＣＣｃｅｌｌ　ｌｉｎｅに対しビタミンＫ－ＩＩ（以下、「ＶＫ－ＩＩ」と称する。）を投与することで細胞の増殖が抑制されること（Ｈｅｐａｔｏｌｏｇｙ　１９９５；２２：８７６－８２）が報告されている。
【０００３】
【発明が解決しようとする課題】
しかしながら、有用な肝疾患治療剤は未だ提供されておらず、特にＰＶＩの発生抑制による肝疾患治療剤は提供されていなかった。
そこで、本発明は、優れた肝疾患治療予防剤を提供することを目的とする。
【０００４】
【発明の構成】
本発明は、ＤＣＰ産生ＨＣＣ患者に対する経口ＶＫ－ＩＩ製剤の投与が、ＨＣＣ治療後のＰＶＩ発生抑制と予後改善に寄与すること、並びに、肝癌の治療後再発を抑制することを初めて見出しなされたものである。
【０００５】
即ち、本発明は、
［１］メナテトレノンを有効成分として含む肝疾患治療・予防剤、
［２］肝疾患が肝癌である前記［１］記載の剤、
［３］肝癌がＤｅｓ－γ－Ｃａｒｂｏｘｙ　Ｐｒｏｔｈｒｏｍｂｉｎ（ＤＣＰ）陽性肝癌である前記［２］記載の剤、
［４］肝癌治療後の予後を改善する前記［１］乃至［３］のいずれか１に記載の剤、
［５］門脈内腫瘍浸潤（ＰＶＩ）の発生抑制剤である前記［４］記載の剤、
［６］メナテトレノンを有効成分として含む門脈内腫瘍浸潤（ＰＶＩ）の発生抑制剤、
［７］メナテトレノンを有効成分として含む肝癌治療後の生存率改善剤、
［８］メナテトレノンを有効成分として含む肝細胞癌の再発抑制剤、
［９］メナテトレノンを有効成分として含むＤＣＰ低下剤、
［１０］メナテトレノンを有効成分として含む医薬を患者に有効量投与することを特徴とする門脈内腫瘍浸潤（ＰＶＩ）の予防方法、
［１１］メナテトレノンを有効成分として含む医薬を患者に有効量投与することを特徴とする肝細胞癌の再発抑制法、
［１２］メナテトレノンを有効成分として含む医薬を患者に有効量投与することを特徴とする血中ＤＣＰ量の調節法、
［１３］ＰＶＩの発生抑制剤製造のためのメナテトレノンの使用、
［１４］肝細胞癌の再発抑制のためのメナテトレノンの使用、および、
［１５］ビタミンＫ類を有効成分として含む肝疾患治療・予防剤に関する。
【０００６】
慢性肝炎、肝硬変からは高率に肝癌が発癌し、いったん発癌すると治療後高率に再発する。例えば、Ｃ型肝炎やＢ型肝炎から肝硬変となり、腫瘍切除後、再発するケースがある。本発明の肝疾患治療剤によれば、このような肝癌治療後の予後を極めて有効に改善（即ち再発の予防又は治療）することができる。また、予後不良な肝癌の再発形態の一つであるＰＶＩの発生を極めて有効に抑制することができる。
【０００７】
メナテトレノンとは、化学名２－メチル－３－テトラプレニル－１，４－ナフトキノン（２－ｍｅｔｈｌ－３－ｔｅｔｒａｐｒｅｎｙｌ－１，４－ｎａｐｈｔｈｏｑｕｉｎｏｎｅ）である。構造式を以下に示す。
【化１】



メナテトレノンは黄色の結晶又は油状の物質で、におい及び味はなく、光により分解しやすい。また、水にはほとんど溶けない。メナテトレノンは、ビタミンＫ－ＩＩ（ＶＫ－ＩＩ）とも称され、その薬理作用は、血液凝固因子（プロトロンビン、ＶＩＩ、ＩＸ、Ｘ）のタンパク合成過程で、グルタミン酸残基が生理活性を有するγ－カルボキシグルタミン酸に変換する際のカルボキシル化反応に関与するものであり、正常プロントロビン等の肝合成を促進し、生体の止血機構を賦活して生理的に止血作用を発現するものである。

【０００８】

本発明にかかる医薬の有効成分であるメナテトレノンは、無水物であってもよいし、水和物を形成していてもよい。また、メナテトレノンには結晶多形が存在することもあるが限定されず、いずれかの結晶形が単一であってもよいし、結晶形混合物であってもよい。さらに、本発明にかかるメナテトレノンが生体内で分解されて生じる代謝物も本発明の特許請求の範囲に包含される。

【０００９】

本発明において用いるメナテトレノンは、自体公知の方法で製造することができ、代表的な例として、特開昭４９－５５６５０号公報に開示される方法によれば容易に製造することができる他、合成メーカーから容易に入手することもできる。また、メナテトレノンはカプセル剤、注射剤等の製剤としても入手できる。本発明にかかる医薬は、メナテトレノンをそのまま用いてもよいし、または、自体公知の薬学的に許容できる担体等（例：賦形剤、結合剤、崩壊剤、滑沢剤、着色剤、矯味矯臭剤、安定化剤、乳化剤、吸収促進剤、界面活性剤、ｐＨ調整剤、防腐剤、抗酸化剤等）、一般に医薬品製剤の原料として用いられる成分を配合して慣用される方法により製剤化してもよい。また、必要に応じて、ビタミン類、アミノ酸、等の成分を配合してもよい。製剤化の剤形としては、錠剤、散剤、細粒剤、顆粒剤、カプセル剤、シロップ剤、坐剤、注射剤、軟膏剤、パップ剤等があげられる。

また、本発明においては、メナテトレノンの投与形態は特に限定されないが、経口的に投与することが好ましい。メナテトレノンのカプセル剤は商品名ケイツーカプセル（エーザイ株式会社製）、グラケーカプセル（エーザイ株式会社製）として、またシロップ剤は商品名ケイツーシロップ（エーザイ株式会社製）として、注射剤は商品名ケイツーＮ注（エーザイ株式会社製）として入手することができる。

本発明にかかるメナテトレノン含有医薬は肝疾患治療・予防に有用である。メナテトレノンの好ましい投与量としては通常は１０～２００ｍｇ／日であり、更に好ましくは３０～１３５ｍｇ／日である。

【００１０】

【実施例】

以下に本発明の試験例を挙げるが、これらは例示的なものであって、本発明はこれらの試験例に限定されるものではない。当業者は、以下に示す試験例のみならず本願明細書にかかる特許請求の範囲に様々な変更を加えて実施することが可能であり、かかる変更も本願特許請求の範囲に包含される。

【００１１】

試験例１

以下のようにして、臨床試験（Ｒａｎｄｏｍｉｚｅｄ　Ｐｒｏｓｐｅｃｔｉｖｅ　Ｃｏｎｔｒｏｌｌｅｄ　Ｓｔｕｄｙ）を行った。

肝癌患者（Ｐａｔｉｅｎｔｓ ｗｉｔｈ Ｈｅｐａｔｏｃｅｌｌｕｌａｒ ｃａｒｃｉｎｏｍａ）のうち、血清ＤＣＰレベルが６０ＩＵ／Ｌより大きいもの（ＤＣＰ陽性肝癌）を試験対象として含めた。一方、門脈浸潤（ｐｏｒｔａｌ ｖｅｎｏｕｓ ｉｎｖａｓｉｏｎ）を伴う患者や、既にビタミンＫ又はアンチビタミンＫ剤投与によるビタミンＫ代謝作用のある患者は試験対象から除外した。試験対象の詳細は表１に示すとおりである。

【表１】

試験対象
対象被験者
1. 肝癌患者
2. 血清 DCP levels ≧ 60 IU/L

対象外被験者
1. 門脈浸潤
2. 肝外転移
3. コントロール不良腹水
4. ビリルビン> 3.0mg/dl
5. Vitamin K 製剤、ワーファリン内服

ＶＫ－ＩＩ投与群
肝癌治療後に vitamin K-II（グラケー）45mg 3X 内服
ＶＫ－ＩＩ非投与群
肝癌の治療のみ
判定
1. 門脈浸潤発生
2. 死亡

【００１２】

図１は、患者の選択フローチャートである。１９９９年２月から２００１年１１月に、１２６人の肝癌患者が治療に供された。肝癌治療としては、ＨＣＣに対して経皮的焼灼療法（ＲＦＡ ａｎｄ／ｏｒ ＰＥＩＴ）、経血管的治療（ＴＡＥ ｏｒＴＡＩ）、外科的切除のいずれかの治療を行った。これらの患者のうち、５人が本実験対象から除外された。次に、１２１人の患者は、無作為に治療群（ｔｒｅａｔｅｄ ｇｒｏｕｐ；ｎ＝６０）と非治療群（ｕｎｔｒｅａｔｅｄ ｇｒｏｕｐ；ｎ＝６１）に分けられた。治療群は、肝癌治療後にＶＫ－ＩＩ（商品名グラケー：エーザイ株式会社製）を４５ｍｇ／日で経口投与される群であり、非治療群は、ＶＫ－ＩＩを投与されない群である。

【００１３】

肝癌治療の後、追跡試験（ｆｏｌｌｏｗ－ｕｐ）を行った。追跡試験は、外来患者に対し、超音波検査（腹部エコー）を３ヶ月毎に行い（ｒｅｃｅｉｖｉｎｇ ｕｌｔｒａｓｏｎｏｇｒａｐｈｙ ｅｖｅｒｙ ３ｍｏｎｔｈｓ），ＣＴスキャン処理を６ヶ月毎に行い（ＣＴ ｓｃａｎ ｅｖｅｒｙ ６ ｍｏｎｔｈｓ）、そしてａｌｆａ－ｆｅｔｏｐｒｏｔｅｉｎとＤＣＰを腫瘍マーカーで１ヶ月毎に測定した。

【００１４】

表２は、患者のプロファイルを示したものである。治療群と非治療群との間で各臨床的パラメータに重要な差は認められなかった。

【００１５】

【表２】

Patients Profile

	Treated(n=60)	Untreated(n=61)	P
年齢	66.9±7.0	67.3±7.5	.8
性（男/女）	36/24	45/16	.12
ウイルス（HCV/non HCV）	50/10	52/9	.81
腫瘍径(mm)	32±11	35±18	.27
腫瘍数	4.0±3.2	4.3±3.5	.66
Child class (A/B or C)	18/42	27/34	.13
アルブミン (g/dl)	3.4±0.5	3.5±0.5	.3
ビリルビン (mg/dl)	1.2±0.7	1.1±0.9	.4
ALT (IU/L)	55±38	61±47	.47
プロトロンビン (%)	78±16	78±14	.99
血小板 ($10^4/mm^3$)	10.8±6.0	11.5±6.6	.52
AFP(ng/L)	2668±7666	1539±7036	.42
DCP(IU/L)	985±2639	1178±5108	.80
PTA with/without	48/12	41/20	.15

Average±SD(Median)

【００１６】
図２は、血清中のＤＣＰレベルの変化を示したグラフである。実線は治療群を表し、点線は非治療群を表している。肝癌治療の後においては、治療群、非治療群の双方において、ＤＣＰレベルが低下した。その後、治療群のＤＣＰレベルは１２ヶ月間ほぼ同様であったのに対して、非治療群のＤＣＰレベルは徐々に増加した。
【００１７】
図３は、ＰＶＩの発生率（Ｉｎｃｉｄｅｎｃｅ ｏｆ ＰＶＩ ｄｅｖｅｌｏｐｍｅｎｔ）の変化を示したグラフである。図３に示すように、治療群においてはＰＶＩ発生率は１年経過後では２％であり、２年経過後では２３％であった。一方、非治療群においては、ＰＶＩ発生率は１年経過後では２３％であり、２年経過後では４７％であった（Ｐ＝０．０１８）。
【００１８】
図４は、生存率（Ｓｕｒｖｉｖａｌ Ｒａｔｅｓ）の変化を示したグラフである。図４に示すように、生存率は治療群においては２年経過後では６６％であり、一方、非治療群においては２年経過後では２８％であった（Ｐ＝０．０４４）。
各群のＰＶＩ発生率、生存率は統計的に処理した。即ちＣｏｘ Ｐｒｏｐｏｒｔｉｏｎａｌ Ｈａｚａｒｄ ｍｏｄｅｌを用いて求め、ｌｏｇ－ｒａｎｋ法により検定した。平均観察期間は１２±８月とした。
以上の結果により、ＶＫ－ＩＩ製剤を経口投与することにより、ＤＣＰ陽性ＨＣＣ患者のＰＶＩ発生率を極めて有効に抑制し、また生存率を極めて増加させ、肝癌治療後の予後を顕著に改善することが示唆された。
【００１９】
試験例２
ＶＫ－ＩＩによる肝細胞癌の治療後再発の抑制効果と安全性を検討する目的で、以下の試験を行った。
即ち、１９９９年３月から２００１年３月に、肝細胞癌と診断され、且つ、その治療後に造影ＣＴにて完全に壊死（または治癒切除）と判断された症例（６１例）をエントリーし

、エントリー症例を、患者ＩＤ番号末尾が奇数をＶＫ－ＩＩ投与群、偶数を非投与群（対照群）の２群に分け、投与群にはＶＫ－ＩＩ製剤（商品名グラケー；エーザイ株式会社製）を４５ｍｇ／日の投与量にて経口投与した。３ヵ月毎に造影ＣＴまたはＭＲＩを行い、再発までの期間を統計的に解析した。即ち、Ｋａｐｌａｎ－Ｍｅｉｅｒ法（Ｌｏｇｒａｎｋ検定）で比較し、再発の危険のある割合（Ｒｉｓｋ　Ｒａｔｉｏ）をＣｏｘ比例ハザードモデルで解析した。

エントリー症例は表３に示すように６１例（投与群３２例、非投与群２９例）で平均観察期間１９．６ヶ月（７－３２）であった。

【００２０】

【表３】

被験患者	投与群（32例）	対照群（29群）
年齢	63.3±7.5（48－75）	64.5±6.7（45－74）
性（M／F）	23／9	18／11
病因（C型/B型/B+C型）	28／3／1	26／2／1
飲酒歴（常習+非常習）	10／22	3／26
初発／再発	15／17	14／15
腫瘍径（mm）	17.7±5.1（10－30）	19.4±6.9（10－38）
腫瘍数	1.50±0.88（1－4）	1.48±0.74（1－3）
Log AFP（ng/ml）	1.47±0.61	1.72±0.91
	（0.60－3.09）	（0.48－3.88）
PIVKA-Ⅱ（mAU/ml）	41.8±65.4	70.3±104.1
	（8－346）	（7－417）
肝機能（LD A/B/C）	15／16／1	13／15／1
治療法（切除／非切除）	1／31	3／26
平均観察期間（月）	24.3±7.1（13－37）	24.2±8.3（12－37）

【００２１】

肝癌の累積再発率を求めたところ、１年再発率が（ＶＫ－ＩＩ投与群）：（対照群）＝１２．５％：５５．２％、２年再発率が（ＶＫ－ＩＩ投与群）：（対照群）＝３９．６％：８５．５％であった。このことから、肝癌の累積再発率は、ＶＫ－ＩＩ投与群において、対照群に比して有意に抑制された。

図５は、肝癌再発抑制（５０％抑制）に対するＶＫ－ＩＩ投与の効果を示したグラフである。図５に示すように、５０％再発までの期間は、ＶＫ－ＩＩ投与群で２６ヶ月であったのに対し、対照群では１０ヶ月であった。

また、ＨＣＶ症例（Ｃ型肝炎症例）に限った場合について、同様に肝癌の累積再発率を求めたところ、１年再発率が（ＶＫ－ＩＩ投与群）：（対照群）＝７．１％：６１．５％、２年再発率が（ＶＫ－ＩＩ投与群）：（対照群）＝３７．８％：８７．２％であった。このことから、ＨＣＶ症例に限った場合においても、肝癌の累積再発率は、ＶＫ－ＩＩ投与群において、対照群に比して有意に抑制された。

図６は、肝癌再発抑制（５０％再発）に対するＶＫ－ＩＩ投与の効果確認試験において、ＨＣＶ症例に限った場合の結果を示したグラフである。図６に示すように、５０％再発までの期間は、ＶＫ－ＩＩ投与群で２６ヶ月であったのに対し、対照群では１０ヶ月であった。

図９は、Ｃｏｘ比例ハザードモデルによって再発危険のある割合（Ｒｉｓｋ　Ｒａｔｉｏ＝ＲＲ）を解析した結果を示した図である。図９に示すように、肝癌再発へのＲｉｓｋ　Ｒａｔｉｏは、対照群を１とした場合、ＶＫ－ＩＩ投与群は０．３２９と約３分の１で、特に、ＨＣＶ症例に限ると、ＶＫ－ＩＩ投与により０．２１０となり、約５分の１に危険性が低下した。

図７は、肝癌再発抑制（５０％抑制）に対するＶＫ－ＩＩ投与の効果確認試験において、局所再発例を除いた場合の結果を示したグラフである（ＶＫ－ＩＩ投与群：２９例、非投与群：２２例）。また、図８は、肝癌再発抑制（５０％抑制）に対するＶＫ－ＩＩ投与の効果のうち、６ヶ月以内の再発例を除いた場合の結果を示すグラフである（ＶＫ－ＩＩ投与群：３１例、非投与群：２２例）。図７及び図８に示すように、これらの場合にも肝癌の累積再発率は、ＶＫ－ＩＩ投与群において、対照群に比して有意に抑制された。

図１０は、治療前と再発時におけるＰＩＶＫＡ－ＩＩを解析した結果を示したグラフである。図１０に示すように、ＶＫ－ＩＩ投与群の再発例では、すべてＰＩＶＫＡ－ＩＩ（Ｐｒｏｔｅｉｎ　Ｉｎｄｕｃｅｄ　ｂｙ　Ｖｉｔａｍｉｎ　Ｋ　Ａｂｓｅｎｃｅ　ｏｒ　Ａｎｔａｇｏｎｉｓｔ）は陰性で、副作用もなく、脱落例も認められなかった。

なお、ＰＩＶＫＡ－ＩＩはＤＣＰとも称され、ビタミンＫ（ＶＫ）の吸収障害、肝実質障害のほか肝細胞癌における代表的な腫瘍マーカーである。

【００２２】

【発明の効果】

本発明にかかるメナテトレノン含有肝疾患治療剤は、肝疾患、特に、ＤＣＰ陽性肝癌に対するＰＶＩの発生抑制効果に優れており、また、肝癌治療後の予後の改善効果に優れている。更に、本発明にかかるメナテトレノン含有肝疾患治療剤は、肝癌の治療後の再発抑制に極めて有用である。

【００２３】

【図面の簡単な説明】

【図１】患者の選別フローチャートである。

【図２】血清中のＤＣＰレベルの変化を示したグラフである。

【図３】ＰＶＩの発生率の変化を示したグラフである。

【図４】生存率の変化を示したグラフである。

【図５】肝癌再発抑制（５０％再発）に対するＶＫ－ＩＩ投与の効果を示したグラフである。

【図６】肝癌再発抑制（５０％再発）に対するＶＫ－ＩＩ投与の効果確認試験において、ＨＣＶ症例のみの結果を示したグラフである。

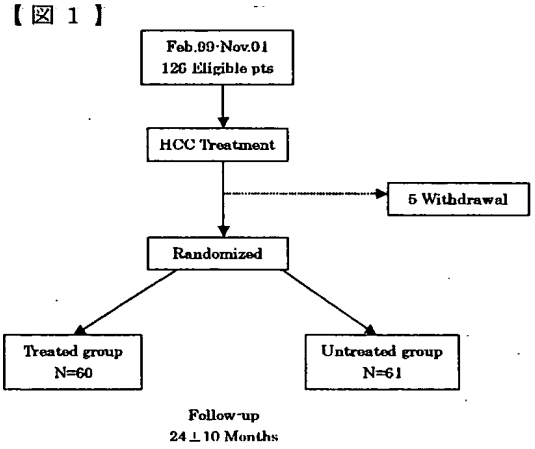
【図７】肝癌再発抑制（５０％再発）に対するＶＫ－ＩＩ投与の効果確認試験において、局所再発例を除いた場合の結果を示したグラフである。

【図８】肝癌再発抑制（５０％再発）に対するＶＫ－ＩＩ投与の効果のうち、６ヶ月以内の再発例を除いた場合の結果を示すグラフである。

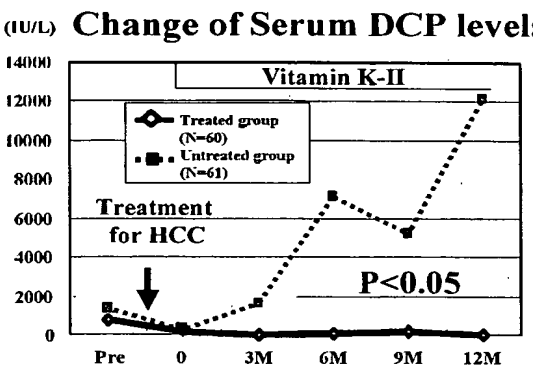
【図９】Ｃｏｘ比例ハザードモデルによって再発危険のある割合（Ｒｉｓｋ　Ｒａｔｉｏ＝ＲＲ）を解析した結果を示した図である。

【図１０】治療前と再発時におけるＰＩＶＫＡ－ＩＩを解析した結果を示したグラフである。

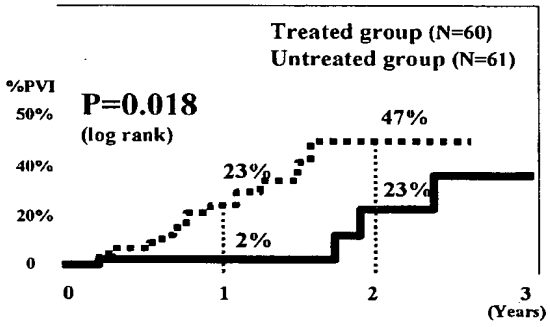
【図１】


Feb.99-Nov.01
126 Eligible pts
HCC Treatment
5 Withdrawal
Randomized
Treated group
N=60
Untreated group
N=61
Follow-up
24±10 Months

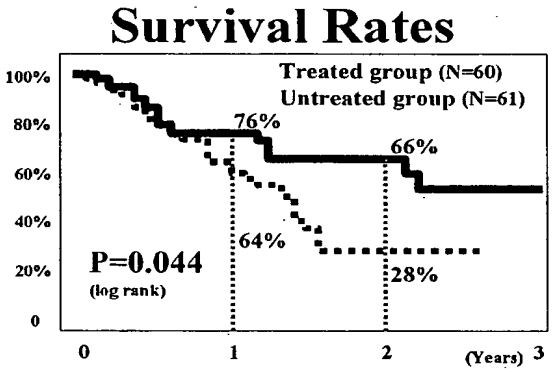
【図２】


(IU/L) Change of Serum DCP levels
Vitamin K-II
Treated group
(N=60)
Untreated group
(N=61)
Treatment
for HCC
P<0.05
14000
12000
10000
8000
6000
4000
2000
0
Pre
0
3M
6M
9M
12M

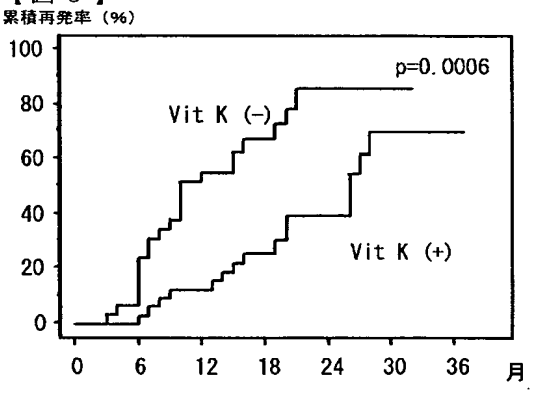
【図３】


Incidence of PVI Development
Treated group (N=60)
Untreated group (N=61)
%PVI
P=0.018
(log rank)
47%
23%
23%
2%
50%
40%
20%
0
0
1
2
3
(Years)

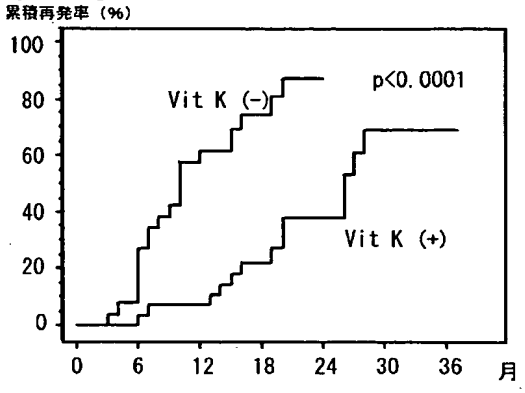
【図４】


Survival Rates
Treated group (N=60)
Untreated group (N=61)
76%
66%
64%
28%
P=0.044
(log rank)
100%
80%
60%
40%
20%
0
0
1
2
(Years)
3

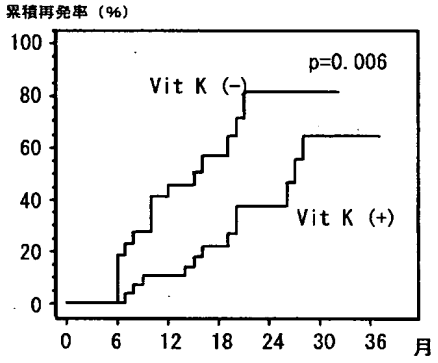
【図５】


累積再発率（%）
p=0.0006
Vit K (-)
Vit K (+)
100
80
60
40
20
0
0
6
12
18
24
30
36
月

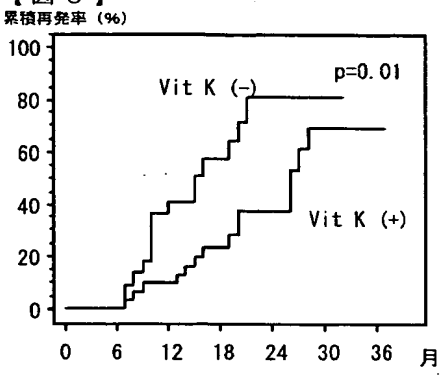
【図６】



【図７】



【図８】



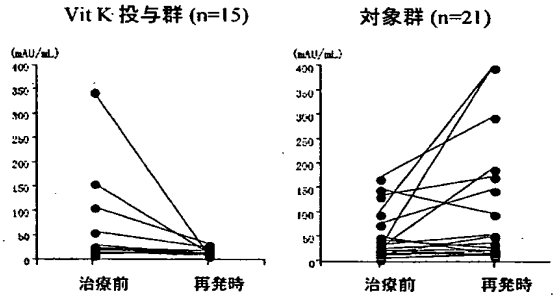
【図９】

Cox比例ハザード・モデルによる肝癌再発のRisk Ratio (RR)

	RR	p	95%C.I.
VK-Ⅱ非投与	1		
全症例			
VK Ⅱ投与	0.329	0.0013	0.167 0.648
VK Ⅱ非投与	1		
HCV症例			
VK-Ⅱ投与	0.210	0.0001	0.094－0.468

【図１０】

治療前と再発時のPIVKA-II



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(54) QUINONE-BASED THERAPEUTIC AGENT FOR HEPATIC DISEASE

(57)Abstract:
PROBLEM TO BE SOLVED: To provide an excellent therapeutic agent for hepatic diseases due to the inhibition of the development of portal venous invasion (PVI).
SOLUTION: The excellent therapeutic and prophylactic agent for hepatic diseases comprises menatetrenone as an active ingredient. The therapeutic and prophylactic agent is especially effective for des-γ-carboxy prothrombin (DCP)-positive hepatic cancer. The therapeutic and prophylactic agent is an inhibitor of the development of the portal venous invasion (PVI) and has remarkable effects on amelioration for prognosis after treating hepatic cancer. Furthermore, the therapeutic and prophylactic agent has excellent effects even as an inhibitor of relapse of the hepatic caner.

LEGAL STATUS

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[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1]
The liver disease therapy and preventive which contains menatetrenone as an active principle.
[Claim 2]
** according to claim 1 whose liver disease is hepatic carcinoma.
[Claim 3]
** according to claim 2 whose hepatic carcinoma is Des-gamma-Carboxy Prothrombin (DCP) positivity hepatic carcinoma.
[Claim 4]
** given in any 1 term of claim 1 which improves the prognosis after a hepatic-carcinoma therapy thru/or claim 3.
[Claim 5]
** according to claim 4 which is a generating inhibitor of the neoplasm infiltration (PVI) in a portal vein.
[Claim 6]
The generating inhibitor of the neoplasm infiltration (PVI) in a portal vein which contains menatetrenone as an active principle.
[Claim 7]
The survival rate improvement agent after the hepatic-carcinoma therapy which contains menatetrenone as an active principle.
[Claim 8]
The recurrence inhibitor of the hepatoma which contains menatetrenone as an active principle.
[Claim 9]
The DCP fall agent which contains menatetrenone as an active principle.
[Claim 10]
The prevention approach of the neoplasm infiltration (PVI) in a portal vein characterized by carrying out effective dose administration of the physic which contains menatetrenone as an active principle at a patient.
[Claim 11]
Recurrence restrainning of the hepatoma characterized by carrying out effective dose administration of the physic which contains menatetrenone as an active principle at a patient.
[Claim 12]
The method of adjusting the amount of DCP(s) in blood characterized by carrying out effective dose administration of the physic which contains menatetrenone as an active principle at a patient.
[Claim 13]
Use of the menatetrenone for generating inhibitor manufacture of PVI.
[Claim 14]
Use of the menatetrenone for recurrence control of the hepatoma.
[Claim 15]
The liver disease therapy and preventive which contains vitamin Ks as an active principle.

[Translation done.]

* NOTICES *

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]
the liver disease therapy agent to which this invention makes menatetrenone an active principle — it is related with a hepatic-carcinoma prognosis improvement agent in more detail.
[0002]
[Description of the Prior Art]
The prognosis is very poor, once it is known that a hepatoma ("HCC" is called hepatocellular carcinoma and the following.) patient will cause portal vein infiltration ("PVI" is called Portal Venous Invasion and the following.) to high rate and PVI occurs. It is known that the high price of Des-gamma-Carboxy Prothrombin ("DCP" is called hereafter.) in a HCC patient is closely connected with subsequent PVI progress here (Koike Y.Cancer 2001; 91:561-9). Here, it is prothrombin without normal coagulation activity, and increasing in the situation that the vitamin K ("VK" is called hereafter.) ran short is known, and DCP is protein used as a marker of lack of VK, and the absorption failure of VK.
On the other hand, it is a vitamin K to HCCcell line of that the DCP value of a blood serum will fall if VK is prescribed for the patient to a DCP high price HCC patient (Cancer 1992; 69:31-8), and the DCP production by in vitro. - It is reported that growth of a cell is controlled by prescribing II ("VK-II" being called hereafter.) for the patient (Hepatology 1995; 22:876-82).
[0003]
[Problem(s) to be Solved by the Invention]
However, the useful liver disease therapy agent was not yet offered, and the liver disease therapy agent especially by generating control of PVI was not offered.
Then, this invention aims at offering the outstanding liver disease therapy preventive.
[0004]
[Elements of the Invention]
This invention finds out controlling the recurrence after a therapy of hepatic carcinoma for the first time in that administration of the oral VK-II pharmaceutical preparation to a DCP production HCC patient contributes to the PVI generating control and the prognosis improvement after a HCC therapy, and a list, and they make it.
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Namely, this invention,
[1] The liver disease therapy and preventive which contains menatetrenone as an active principle,
[2] ** of the aforementioned [1] publication whose liver disease is hepatic carcinoma,
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[4] The above [1] which improves the prognosis after a hepatic-carcinoma therapy thru/or ** given in any 1 of [3],
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[15] It is related with the liver disease therapy and preventive which contains vitamin Ks as an active principle.
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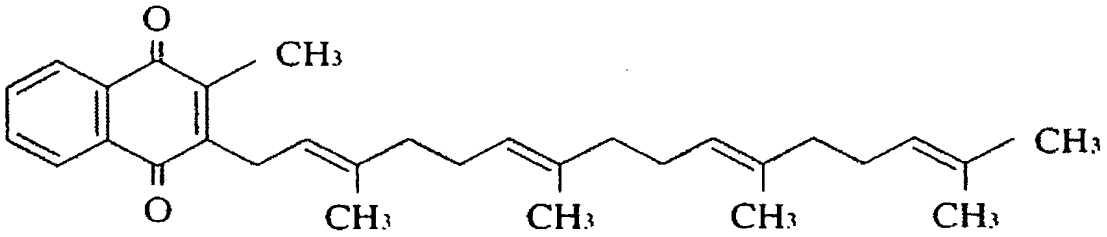
From the chronic hepatitis and liver cirrhosis, once hepatic carcinoma carries out oncogenesis and carries out oncogenesis to high rate, it will recur to the high rate after a therapy. For example, it becomes liver cirrhosis from hepatitis C or hepatitis B, and there is a case which recurs after neoplasm excision. According to the liver disease therapy agent of this invention, the prognosis after such a hepatic-carcinoma therapy can be improved very effectively (namely, prevention or the therapy of a recurrence). Moreover, generating of PVI which is one of the recurrence gestalten of hepatic carcinoma with a poor prognosis can be controlled very effectively.
[0007]
Menatetrenone is chemical name 2-methyl-3-tetra-prenyl-1,4-naphthoquinone (2-methl-3-tetraprenyl-1, 4-naphthoquinone). A structure expression is shown below.
[Formula 1]



Menatetrenone is a yellow crystal or the oil-like matter, there are not a smell and a taste and light is easy to decompose them. Moreover, it hardly melts into water. what participates in the carboxylation reaction at the time of changing into the gamma-carboxyglutamic acid in which menatetrenone is also called vitamin K-II (VK-II), the pharmacological action is the protein composition process of a blood coagulation factor (prothrombin, VII, IX, X), and glutamic-acid residue has bioactive — it is — a normal prong — fatty tuna — liver composition of a bottle etc. is promoted, activation of a living body's mechanism of hemostasis is carried out, and a hemostatic action is discovered physiologically.
[0008]
The menatetrenone which is a medicinal active principle concerning this invention may be an anhydride, and may form the hydrate. Moreover, although a crystal polymorphism may exist in menatetrenone, it may not be limited, but one of crystal form may be single, and you may be crystal form mixture. Furthermore, the metabolite which it is decomposed in the living body and the menatetrenone concerning this invention produces is also included by the claim of this invention.
[0009]
the menatetrenone used in this invention — the very thing — it can manufacture by the well-known approach, and according to the approach indicated by JP,49-55650,A, it can manufacture easily as a typical example, and also can also obtain easily from a synthetic manufacturer. Moreover, menatetrenone can come to hand also as pharmaceutical preparation, such as a capsule and injections. the physic concerning this invention — menatetrenone — as it is — you may use — or the very thing — well-known pharmacologically permissible support etc. may be pharmaceutical-preparation-ized by the approach which blends the components (example: an excipient, a binder, disintegrator, lubricant, a coloring agent, correctives, a stabilizing agent, an emulsifier,

absorption enhancers, a surfactant, pH regulator, antiseptics, anti-oxidant, etc.) generally used as a raw material of drugs pharmaceutical preparation, and is used commonly. Moreover, components, such as vitamins and amino acid, may be blended if needed. As dosage forms of pharmaceutical-preparation-izing, a tablet, powder, a fine grain agent, a granule, a capsule, syrups, suppositories, injections, an ointment, cataplasms, etc. are raised. Moreover, in this invention, although especially the administration gestalt of menatetrenone is not limited, it is desirable to prescribe a medicine for the patient in taking orally. The syrups as a trade name Kaytwo capsule (Eisai Co., Ltd. make) and a Glakay capsule (Eisai Co., Ltd. make) can obtain as trade name Kaytwo syrup (Eisai Co., Ltd. make), and the capsule of menatetrenone can obtain injections as trade name Kaytwo N notes (Eisai Co., Ltd. make).
The menatetrenone content physic concerning this invention is useful to a liver disease therapy and prevention. As a desirable dose of menatetrenone, it is usually 10-200mg/day, and is 30-135mg/day still more preferably.
[0010]
[Example]
Although the example of a trial of this invention is given to below, and this invention is not limited to these examples of a trial. [these] [instantiation] this contractor adds and carries out various modification to the claim not only concerning the example of a trial shown below but this application specification — possible — this modification — this application — it is included by the claim.
[0011]
The example 1 of a trial
As it was the following, the clinical trial (Randomized Prospective Controlled Study) was performed.
What has the larger blood serum DCP level among hepatic-carcinoma patients (Patients with Hepatocellular carcinoma) than 60 IU/L (DCP positivity hepatic carcinoma) was included as a test objective. On the other hand, the patient accompanied by portal vein infiltration (portal venous invasion) and the patient who already has the vitamin K metabolism by vitamin K or antivitamin K agent administration excepted from the test objective. The detail of a test objective is as being shown in Table 1.
[Table 1]

試験対象
対象被験者
1. 肝癌患者
2. 血清 DCP levels ≧ 60 IU/L
対象外被験者
1. 門脈浸潤
2. 肝外転移
3. コントロール不良腹水
4. ビリルビン> 3.0mg/dl
5. Vitamin K製剤、ワーファリン内服

ＶＫ－ＩＩ投与群
肝癌治療後に vitamin K-II (グラケー)45mg 3X 内服
ＶＫ－ＩＩ非投与群
肝癌の治療のみ
判定
1. 門脈浸潤発生
2. 死亡

[0012]
Drawing 1 is a patient's selection flow chart. The therapy was presented with 126 hepatic-carcinoma patients from February, 1999 in November, 2001. As a hepatic-carcinoma therapy, the endermic cautery therapy (RFA and/or PEIT), the menstrual blood tubing-therapy (TAE orTAI), or the surgical resection was treated to HCC. Five of these patients were excepted from this candidate for an experiment.
Next, 121 patients were divided into the therapy group (treated group;n=60) and the non-treating group

(untreated group;n=61) at random. A therapy group is a group to which VK-II (trade-name Glakay: Eisai Co., Ltd. make) will be administered orally in a day in-45mg /after a hepatic-carcinoma therapy, and a non-treating group is a group which is not medicated with VK-II.

[0013]

The trace trial (follow-up) was performed after the hepatic-carcinoma therapy. To the outpatient, the trace trial conducted the ultrasonic examination (abdomen echo) every three months (receiving ultrasonography every 3months), and performed CT scanning and processing every six months (CT scan every 6 months), and measured alfa-fetoprotein and DCP for every month by the tumor marker.

[0014]

Table 2 shows a patient's profile. The difference important for each clinical parameter between a therapy group and a non-treating group was not accepted.

[0015]

[Table 2]

Patients Profile

	Treated(n=60)	Untreated(n=61)	P
年齢	66.9±7.0	67.3±7.5	.8
性（男/女）	36/24	45/16	.12
ウイルス (HCV/non HCV)	50/10	52/9	.81
腫瘍径(mm)	32±11	35±18	.27
腫瘍数	4.0±3.2	4.3±3.5	.66
Child class (A/B or C)	18/42	27/34	.13
アルブミン (g/dl)	3.4±0.5	3.5±0.5	.3
ビリルビン (mg/dl)	1.2±0.7	1.1±0.9	.4
ALT (IU/L)	55±38	61±47	.47
プロトロンビン (%)	78±16	78±14	.99
血小板 ($10^4/mm^3$)	10.8±6.0	11.5±6.6	.52
AFP(ng/L)	2668±7666	1539±7036	.42
DCP(IU/L)	985±2639	1178±5108	.80
PTA with/without	48/12	41/20	.15

Average±SD(Median)

[0016]

Drawing 2 is the graph which showed change of the DCP level in a blood serum. A continuous line expresses a therapy group and the dotted line expresses the non-treating group. In after a hepatic-carcinoma therapy, DCP level fell in the both sides of a therapy group and a non-treating group. Then, the DCP level of a non-treating group increased gradually to having been almost the same for 12 months as for the DCP level of a therapy group.

[0017]

Drawing 3 is the graph which showed change of the incidence rate (Incidence of PVI development) of PVI. As shown in drawing 3 , in the therapy group, the PVI incidence rate was 2% after one-year progress, and was 23% after two-year progress. On the other hand, in the non-treating group, the PVI incidence rate was 23% after one-year progress, and was 47% after two-year progress (P= 0.018).

[0018]

Drawing 4 is the graph which showed change of a survival rate (Survival Rates). As shown in drawing 4 , the survival rate was 66% after two-year progress in the therapy group, and, on the other hand, was 28% after two-

year progress in the non-treating group (P= 0.044).
The PVI incidence rate of each group and the survival rate were processed statistically. namely, Cox Proportional Hazard model — using — asking — log-rank — it authorized by law. The average observation period was made into 12 August [**].
Controlling very effectively a DCP positivity HCC patient's PVI incidence rate, and making a survival rate increase extremely, and improving the prognosis after a hepatic-carcinoma therapy notably by administering VK-II pharmaceutical preparation orally, by the above result, was suggested.
[0019]
The example 2 of a trial
The following trials were performed in order to examine the depressor effect and the safety of the recurrence after a therapy of the hepatoma by VK-II.
Namely, it will diagnose as the hepatoma from March, 1999 in March, 2001. And the case (61 examples) completely judged to be a necrosis (or curative resection) by Imaging CT after the therapy is entered. The patient ID number tail divided odd number into the VK-II administration group, and divided even number into 2 of the group (control group) non-prescribing a medicine for the patient groups for the entry case, and VK-II pharmaceutical preparation (trade name Glakay; Eisai Co., Ltd. make) was administered orally to the administration group with the dose of 45mg/day. Imaging CT or MRI was performed every three months, and the period to a recurrence was analyzed statistically. That is, it compared with the Kaplan-Meier method (Logrank assay), and the rate (Risk Ratio) with the risk of a recurrence was analyzed by the Cox proportional hazard model.
The entry case was average observation period 19.6 months (7-32) in 61 examples (32 administration groups, 29 groups non-prescribing a medicine for the patient), as shown in Table 3.
[0020]
[Table 3]

被験患者	投与群 (32例)	対照群 (29群)
年齢	63.3±7.5 (48−75)	64.5±6.7 (45−74)
性 (M/F)	23/9	18/11
病因 (C型/B型/B+C型)	28/3/1	26/2/1
飲酒歴 (常習+非常習)	10/22	3/26
初発/再発	15/17	14/15
腫瘍径 (mm)	17.7±5.1 (10−30)	19.4±6.9 (10−38)
腫瘍数	1.50±0.88 (1−4)	1.48±0.74 (1−3)
Log AFP (ng/ml)	1.47±0.61	1.72±0.91
	(0.60−3.09)	(0.48−3.88)
PIVKA-II (mAU/ml)	41.8±65.4	70.3±104.1
	(8−346)	(7−417)
肝機能 (LD A/B/C)	15/16/1	13/15/1
治療法 (切除/非切除)	1/31	3/26
平均観察期間 (月)	24.3±7.1 (13−37)	24.2±8.3 (12−37)

[0021]
When the accumulation recurrence rate of hepatic carcinoma was searched for, the one-year recurrence rate was :(VK-II administration group) (control group) =12.5%:55.2%, and the two-year recurrence rate was :(VK-II administration group) (control group) =39.6%:85.5%. From this, the accumulation recurrence rate of hepatic carcinoma was intentionally controlled in the VK-II administration group as compared with the control group.
Drawing 5 is the graph which showed the effectiveness of VK-II administration over hepatic-carcinoma recurrence control (50% control). As shown in drawing 5 , the period to 50% recurrence was ten months in the control group to having been 26 months by the VK-II administration group.
Moreover, when the accumulation recurrence rate of hepatic carcinoma was similarly searched for about the case where it restricts to a HCV case (example of C type liver inflammation), the one-year recurrence rate was : (VK-II administration group) (control group) =7.1%:61.5%, and the two-year recurrence rate was :(VK-II administration group) (control group) =37.8%:87.2%. From this, when it restricted to a HCV case, the accumulation recurrence rate of hepatic carcinoma was intentionally controlled in the VK-II administration group as compared with the control group.
Drawing 6 is the graph which showed the result at the time of restricting to a HCV case in the effectiveness verification test of the VK-II administration to hepatic-carcinoma recurrence control (50% recurrence). As shown in drawing 6 , the period to 50% recurrence was ten months in the control group to having been 26 months by the VK-II administration group.
Drawing 9 is drawing having shown the result of having analyzed the rate (Risk Ratio=RR) with recurrence risk by the Cox proportional hazard model. When Risk Ratio to a hepatic-carcinoma recurrence set a control group to 1, and VK-II administration groups are 0.329 and about 1/3 and it restricted to the HCV case especially, it was set to 0.210 by VK-II administration, and danger fell [as shown in drawing 9 ,] to about 1/5.
Drawing 7 is the graph which showed the result at the time of removing the example of a local recurrence in the effectiveness verification test of the VK-II administration to hepatic-carcinoma recurrence control (50% control) (VK-II administration group: 29 examples, group non-prescribing a medicine for the patient : 22 examples).
Moreover, drawing 8 is a graph which shows the result at the time of removing the example of a recurrence for less than six months among the effectiveness of VK-II administration over hepatic-carcinoma recurrence control (50% control) (VK-II administration group: 31 examples, group non-prescribing a medicine for the patient : 22 examples). As shown in drawing 7 and drawing 8 , the accumulation recurrence rate of hepatic carcinoma was intentionally controlled in the VK-II administration group as compared with the control group also in these cases.

Drawing 10 is the graph which showed the result of having analyzed PIVKA-II at the time of a recurrence therapy before. As shown in drawing 10 , in the example of a recurrence of a VK-II administration group, altogether, PIVKA-II (Protein Induced by Vitamin K Absence or Antagonist) is negative, and does not have a side effect, either, and the example of omission was not accepted, either.
In addition, PIVKA-II is also called DCP and is a typical tumor marker in the hepatoma besides the absorption failure of a vitamin K (VK), and a liver parenchyma failure.
[0022]
[Effect of the Invention]
The menatetrenone content liver disease therapy agent concerning this invention is excellent in the generating depressor effect of liver disease and PVI [especially as opposed to DCP positivity hepatic carcinoma], and excellent in the improvement effect of the prognosis after a hepatic-carcinoma therapy. Furthermore, the menatetrenone content liver disease therapy agent concerning this invention is very useful to the recurrence control after the therapy of hepatic carcinoma.
[0023]
[Brief Description of the Drawings]
[Drawing 1] It is a patient's sorting flow chart.
[Drawing 2] It is the graph which showed change of the DCP level in a blood serum.
[Drawing 3] It is the graph which showed change of the incidence rate of PVI.
[Drawing 4] It is the graph which showed change of a survival rate.
[Drawing 5] It is the graph which showed the effectiveness of VK-II administration over hepatic-carcinoma recurrence control (50% recurrence).

[Drawing 6] In the effectiveness verification test of the VK-II administration to hepatic-carcinoma recurrence control (50% recurrence), it is the graph which showed the result of only a HCV case.
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TECHNICAL FIELD

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PRIOR ART

[Description of the Prior Art]
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TECHNICAL PROBLEM

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However, the useful liver disease therapy agent was not yet offered, and the liver disease therapy agent especially by generating control of PVI was not offered.
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Menatetrenone is chemical name 2-methyl-3-tetra-prenyl-1,4-naphthoquinone (2-methl-3-tetraprenyl-1, 4-naphthoquinone). A structure expression is shown below.
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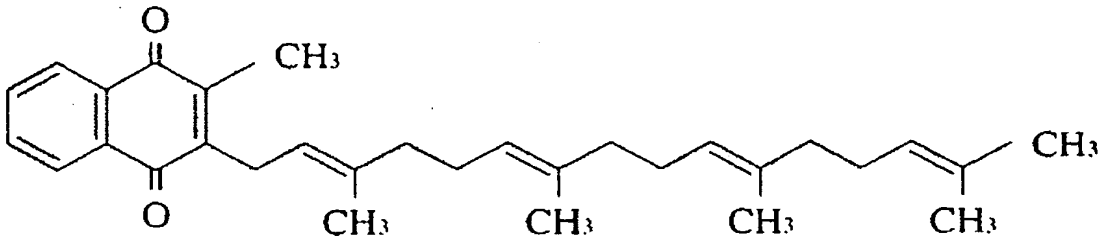

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The menatetrenone which is a medicinal active principle concerning this invention may be an anhydride, and may form the hydrate. Moreover, although a crystal polymorphism may exist in menatetrenone, it may not be limited, but one of crystal form may be single, and you may be crystal form mixture. Furthermore, the metabolite which it is decomposed in the living body and the menatetrenone concerning this invention produces is also included by the claim of this invention.
[0009]
the menatetrenone used in this invention — the very thing — it can manufacture by the well-known approach, and according to the approach indicated by JP,49-55650,A, it can manufacture easily as a typical example, and also can also obtain easily from a synthetic manufacturer. Moreover, menatetrenone can come to hand also as pharmaceutical preparation, such as a capsule and injections. the physic concerning this invention — menatetrenone — as it is — you may use — or the very thing — well-known pharmacologically permissible support etc. may be pharmaceutical-preparation-ized by the approach which blends the components (example: an excipient, a binder, disintegrator, lubricant, a coloring agent, correctives, a stabilizing agent, an emulsifier, absorption enhancers, a surfactant, pH regulator, antiseptics, anti-oxidant, etc.) generally used as a raw material of drugs pharmaceutical preparation, and is used commonly. Moreover, components, such as vitamins and amino acid, may be blended if needed. As dosage forms of pharmaceutical-preparation-izing, a tablet, powder, a fine grain agent, a granule, a capsule, syrups, suppositories, injections, an ointment, cataplasms, etc. are raised. Moreover, in this invention, although especially the administration gestalt of menatetrenone is not limited, it is desirable to prescribe a medicine for the patient in taking orally. The syrups as a trade name Kaytwo capsule (Eisai Co., Ltd. make) and a Glakay capsule (Eisai Co., Ltd. make) can obtain as trade name Kaytwo syrup (Eisai Co., Ltd. make), and the capsule of menatetrenone can obtain injections as trade name Kaytwo N notes (Eisai Co., Ltd. make).
The menatetrenone content physic concerning this invention is useful to a liver disease therapy and prevention. As a desirable dose of menatetrenone, it is usually 10-200mg/day, and is 30-135mg/day still more preferably.
[0010]

[Translation done.]

EXAMPLE

[Example]
Although the example of a trial of this invention is given to below, and this invention is not limited to these examples of a trial. [these] [instantiation] this contractor adds and carries out various modification to the claim not only concerning the example of a trial shown below but this application specification — possible — this modification — this application — it is included by the claim.
[0011]
The example 1 of a trial
As it was the following, the clinical trial (Randomized Prospective Controlled Study) was performed.
What has the larger blood serum DCP level among hepatic-carcinoma patients (Patients with Hepatocellular carcinoma) than 60 IU/L (DCP positivity hepatic carcinoma) was included as a test objective. On the other hand, the patient accompanied by portal vein infiltration (portal venous invasion) and the patient who already has the vitamin K metabolism by vitamin K or antivitamin K agent administration excepted from the test objective. The detail of a test objective is as being shown in Table 1.
[Table 1]

試験対象
対象被験者
1. 肝癌患者
2. 血清 DCP levels ≥ 60 IU/L
対象外被験者
1. 門脈浸潤
2. 肝外転移
3. コントロール不良腹水
4. ビリルビン> 3.0mg/dl
5. Vitamin K製剤、ワーファリン内服

ＶＫ－ＩＩ投与群
肝癌治療後に vitamin K-II (グラケー)45mg 3X 内服
ＶＫ－ＩＩ非投与群
肝癌の治療のみ
判定
1. 門脈浸潤発生
2. 死亡

[0012]
Drawing 1 is a patient's selection flow chart. The therapy was presented with 126 hepatic-carcinoma patients from February, 1999 in November, 2001. As a hepatic-carcinoma therapy, the endermic cautery therapy (RFA and/or PEIT), the menstrual blood tubing-therapy (TAE orTAI), or the surgical resection was treated to HCC. Five of these patients were excepted from this candidate for an experiment.
Next, 121 patients were divided into the therapy group (treated group;n=60) and the non-treating group (untreated group;n=61) at random. A therapy group is a group to which VK-II (trade-name Glakay: Eisai Co., Ltd.

make) will be administered orally in a day in 45mg /after a hepatic-carcinoma therapy, and a non-treating group is a group which is not medicated with VK-II.

[0013]

The trace trial (follow-up) was performed after the hepatic-carcinoma therapy. To the outpatient, the trace trial conducted the ultrasonic examination (abdomen echo) every three months (receiving ultrasonography every 3months), and performed CT scanning and processing every six months (CT scan every 6 months), and measured alfa-fetoprotein and DCP for every month by the tumor marker.

[0014]

Table 2 shows a patient's profile. The difference important for each clinical parameter between a therapy group and a non-treating group was not accepted.

[0015]

[Table 2]

Patients Profile

	Treated(n=60)	Untreated(n=61)	P
年齢	66.9±7.0	67.3±7.5	.8
性 (男/女)	36/24	45/16	.12
ウイルス (HCV/non HCV)	50/10	52/9	.81
腫瘍径(mm)	32±11	35±18	.27
腫瘍数	4.0±3.2	4.3±3.5	.66
Child class (A/B or C)	18/42	27/34	.13
アルブミン (g/dl)	3.4±0.5	3.5±0.5	.3
ビリルビン (mg/dl)	1.2±0.7	1.1±0.9	.4
ALT (IU/L)	55±38	61±47	.47
プロトロンビン (%)	78±16	78±14	.99
血小板 ($10^4/mm^3$)	10.8±6.0	11.5±6.6	.52
AFP(ng/L)	2668±7666	1539±7036	.42
DCP(IU/L)	985±2639	1178±5108	.80
PTA with/without	48/12	41/20	.15

Average±SD(Median)

[0016]

Drawing 2 is the graph which showed change of the DCP level in a blood serum. A continuous line expresses a therapy group and the dotted line expresses the non-treating group. In after a hepatic-carcinoma therapy, DCP level fell in the both sides of a therapy group and a non-treating group. Then, the DCP level of a non-treating group increased gradually to having been almost the same for 12 months as for the DCP level of a therapy group.

[0017]

Drawing 3 is the graph which showed change of the incidence rate (Incidence of PVI development) of PVI. As shown in drawing 3 , in the therapy group, the PVI incidence rate was 2% after one-year progress, and was 23% after two-year progress. On the other hand, in the non-treating group, the PVI incidence rate was 23% after one-year progress, and was 47% after two-year progress (P= 0.018).

[0018]

Drawing 4 is the graph which showed change of a survival rate (Survival Rates). As shown in drawing 4 , the survival rate was 66% after two-year progress in the therapy group, and, on the other hand, was 28% after two-year progress in the non-treating group (P= 0.044).

The PVI incidence rate of each group and the survival rate were processed statistically. namely, Cox Proportional Hazard model — using — asking — log-rank — it authorized by law. The average observation period was made into 12 August [**].
Controlling very effectively a DCP positivity HCC patient's PVI incidence rate, and making a survival rate increase extremely, and improving the prognosis after a hepatic-carcinoma therapy notably by administering VK-II pharmaceutical preparation orally, by the above result, was suggested.
[0019]
The example 2 of a trial
The following trials were performed in order to examine the depressor effect and the safety of the recurrence after a therapy of the hepatoma by VK-II.
Namely, it will diagnose as the hepatoma from March, 1999 in March, 2001. And the case (61 examples) completely judged to be a necrosis (or curative resection) by Imaging CT after the therapy is entered. The patient ID number tail divided odd number into the VK-II administration group, and divided even number into 2 of the group (control group) non-prescribing a medicine for the patient groups for the entry case, and VK-II pharmaceutical preparation (trade name Glakay; Eisai Co., Ltd. make) was administered orally to the administration group with the dose of 45mg/day. Imaging CT or MRI was performed every three months, and the period to a recurrence was analyzed statistically. That is, it compared with the Kaplan-Meier method (Logrank assay), and the rate (Risk Ratio) with the risk of a recurrence was analyzed by the Cox proportional hazard model.
The entry case was average observation period 19.6 months (7-32) in 61 examples (32 administration groups, 29 groups non-prescribing a medicine for the patient), as shown in Table 3.
[0020]
[Table 3]

被験患者	投与群 (32例)	対照群 (29群)
年齢	63.3±7.5 (48－75)	64.5±6.7 (45－74)
性 (M／F)	23／9	18／11
病因 (C型/B型/B+C型)	28／3／1	26／2／1
飲酒歴 (常習+非常習)	10／22	3／26
初発／再発	15／17	14／15
腫瘍径 (mm)	17.7±5.1 (10－30)	19.4±6.9 (10－38)
腫瘍数	1.50±0.88 (1－4)	1.48±0.74 (1－3)
Log AFP (ng/ml)	1.47±0.61	1.72±0.91
	(0.60－3.09)	(0.48－3.88)
PIVKA-II (mAU/ml)	41.8±65.4	70.3±104.1
	(8－346)	(7－417)
肝機能 (LD A/B/C)	15／16／1	13／15／1
治療法 (切除／非切除)	1／31	3／26
平均観察期間 (月)	24.3±7.1 (13－37)	24.2±8.3 (12－37)

[0021]
When the accumulation recurrence rate of hepatic carcinoma was searched for, the one-year recurrence rate was :(VK-II administration group) (control group) =12.5%:55.2%, and the two-year recurrence rate was :(VK-II administration group) (control group) =39.6%:85.5%. From this, the accumulation recurrence rate of hepatic carcinoma was intentionally controlled in the VK-II administration group as compared with the control group.
Drawing 5 is the graph which showed the effectiveness of VK-II administration over hepatic-carcinoma recurrence control (50% control). As shown in drawing 5 , the period to 50% recurrence was ten months in the control group to having been 26 months by the VK-II administration group.
Moreover, when the accumulation recurrence rate of hepatic carcinoma was similarly searched for about the case where it restricts to a HCV case (example of C type liver inflammation), the one-year recurrence rate was : (VK-II administration group) (control group) =7.1%:61.5%, and the two-year recurrence rate was :(VK-II administration group) (control group) =37.8%:87.2%. From this, when it restricted to a HCV case, the accumulation recurrence rate of hepatic carcinoma was intentionally controlled in the VK-II administration group as compared with the control group.
Drawing 6 is the graph which showed the result at the time of restricting to a HCV case in the effectiveness verification test of the VK-II administration to hepatic-carcinoma recurrence control (50% recurrence). As shown in drawing 6 , the period to 50% recurrence was ten months in the control group to having been 26 months by the VK-II administration group.
Drawing 9 is drawing having shown the result of having analyzed the rate (Risk Ratio=RR) with recurrence risk by the Cox proportional hazard model. When Risk Ratio to a hepatic-carcinoma recurrence set a control group to 1, and VK-II administration groups are 0.329 and about 1/3 and it restricted to the HCV case especially, it was set to 0.210 by VK-II administration, and danger fell [as shown in drawing 9 ,] to about 1/5.
Drawing 7 is the graph which showed the result at the time of removing the example of a local recurrence in the effectiveness verification test of the VK-II administration to hepatic-carcinoma recurrence control (50% control) (VK-II administration group: 29 examples, group non-prescribing a medicine for the patient : 22 examples).
Moreover, drawing 8 is a graph which shows the result at the time of removing the example of a recurrence for less than six months among the effectiveness of VK-II administration over hepatic-carcinoma recurrence control (50% control) (VK-II administration group: 31 examples, group non-prescribing a medicine for the patient : 22 examples). As shown in drawing 7 and drawing 8 , the accumulation recurrence rate of hepatic carcinoma was intentionally controlled in the VK-II administration group as compared with the control group also in these cases.

Drawing 10 is the graph which showed the result of having analyzed PIVKA-II at the time of a recurrence therapy before. As shown in drawing 10 , in the example of a recurrence of a VK-II administration group, altogether, PIVKA-II (Protein Induced by Vitamin K Absence or Antagonist) is negative, and does not have a side effect, either, and the example of omission was not accepted, either.
In addition, PIVKA-II is also called DCP and is a typical tumor marker in the hepatoma besides the absorption failure of a vitamin K (VK), and a liver parenchyma failure.
[0022]

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

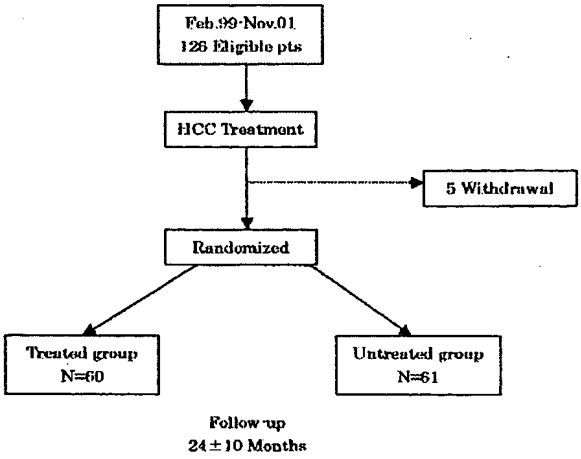
DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1] It is a patient's sorting flow chart.
[Drawing 2] It is the graph which showed change of the DCP level in a blood serum.
[Drawing 3] It is the graph which showed change of the incidence rate of PVI.
[Drawing 4] It is the graph which showed change of a survival rate.
[Drawing 5] It is the graph which showed the effectiveness of VK-II administration over hepatic-carcinoma recurrence control (50% recurrence).
[Drawing 6] In the effectiveness verification test of the VK-II administration to hepatic-carcinoma recurrence control (50% recurrence), it is the graph which showed the result of only a HCV case.
[Drawing 7] In the effectiveness verification test of the VK-II administration to hepatic-carcinoma recurrence control (50% recurrence), it is the graph which showed the result at the time of removing the example of a local recurrence.
[Drawing 8] It is the graph which shows the result at the time of removing the example of a recurrence for less than six months among the effectiveness of VK-II administration over hepatic-carcinoma recurrence control (50% recurrence).
[Drawing 9] It is drawing having shown the result of having analyzed the rate (Risk Ratio=RR) with recurrence risk by the Cox proportional hazard model.
[Drawing 10] It is the graph which showed the result of having analyzed PIVKA-II at the time of a recurrence therapy before.

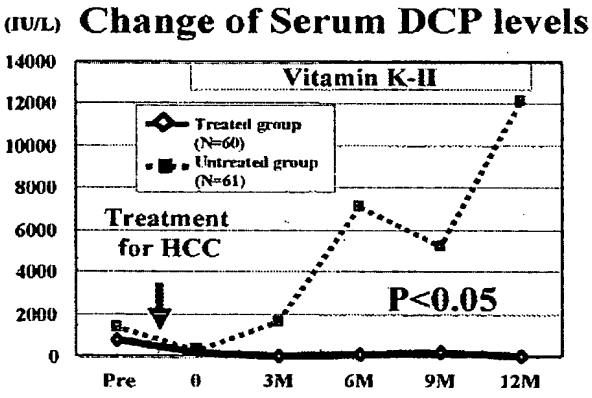
[Translation done.]

DRAWINGS

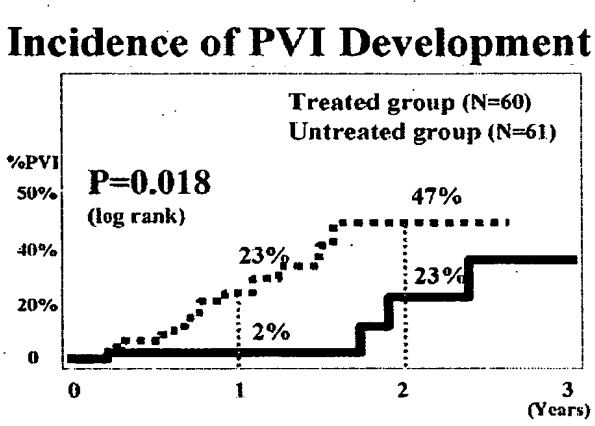
[Drawing 1]



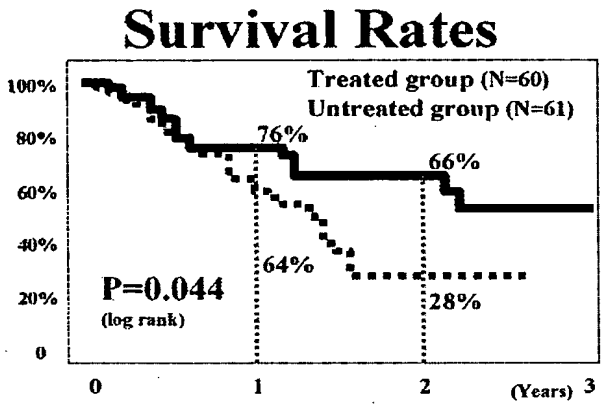
[Drawing 2]



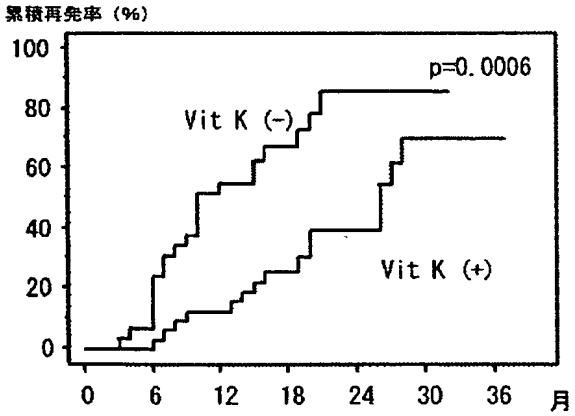
[Drawing 3]



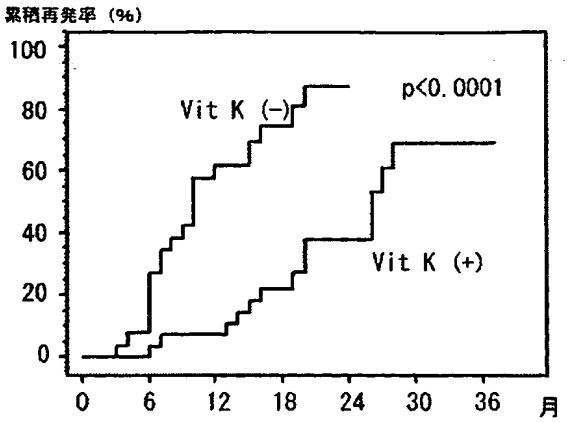
[Drawing 4]



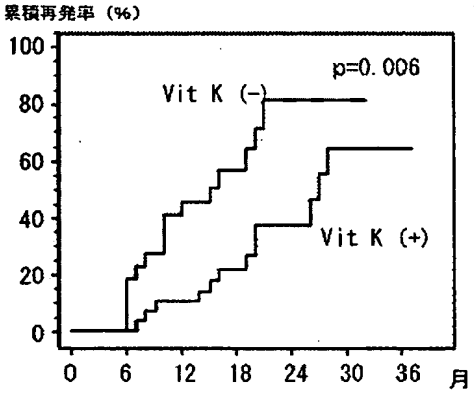
[Drawing 5]



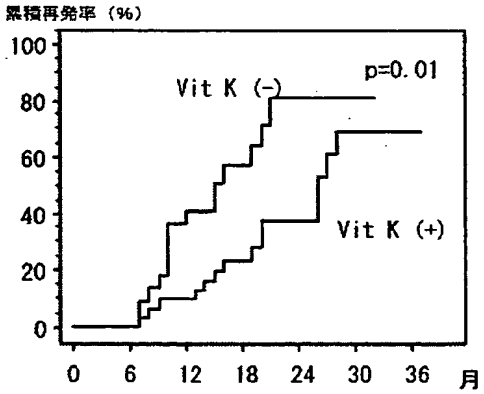
[Drawing 6]



[Drawing 7]



[Drawing 8]



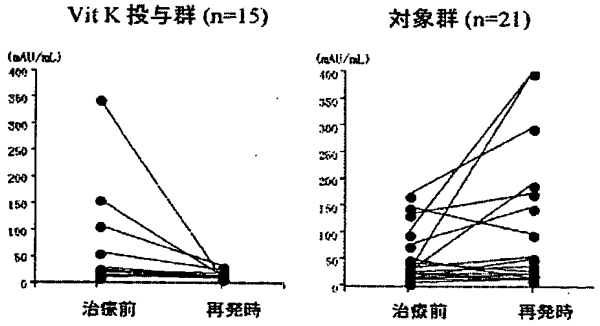
[Drawing 9]

Cox比例ハザードモデルによる肝癌再発のRisk Ratio (RR)

	RR	p	95%C. I.
VK-II非投与	1		
全症例			
VK-II投与	0.329	0.0013	0.167－0.648
VK-II非投与	1		
HCV症例			
VK-II投与	0.210	0.0001	0.094－0.468

[Drawing 10]

治療前と再発時のPIVKA-II



[Translation done.]